Criteria for Non-Formulary Use of Quinine Sulfate in Nocturnal Leg Cramps

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

These criteria were developed using the best evidence currently available. The following recommendations are dynamic and will be revised as new clinical data becomes available. These guidelines are not intended to interfere with clinical judgment. Rather, they are intended to assist practitioners in providing consistent, high quality care.

I. Background

For decades, quinine sulfate has been commonly prescribed for the prophylaxis and treatment of leg cramps. A survey at the Denver VAMC reported symptoms of nocturnal leg cramps in 56% of 515 male veterans. [1] Although only 36% of the patients reported drug treatment for their cramps, quinine was reported as effective in 50% of those receiving it. From 1969 through June 1992, one hundred and fifty-seven reports of side effects related to quinine use were reported to the FDA. The reports consisted of sight disturbances, dizziness, cinchonism (nausea, vomiting, tinnitus, and deafness), fever, diarrhea, thrombocytopenia, and 23 reports of death.[2] In August of 1994 the FDA published a rule prohibiting the OTC (and in 1995 the prescription) marketing of quinine sulfate for leg cramps, due to a lack of efficacy data and risks that outweigh its potential benefits for a non life-threatening condition.[3] After further review, the FDA halted OTC marketing of quinine for malaria in 1998.[4] Numerous studies were performed after quinine lost its FDA indication, and despite their limitations and varied determinants of efficacy, quinine remains the most widely used treatment for leg cramps.

II. Indications for VA Patients

In 1994 Man-Son Hing et al. performed a meta-analysis to quantitatively assess quinine's efficacy compared with placebo for nocturnal leg cramps.[5] They concluded that quinine can reduce and prevent the number of events with a 43% relative risk reduction (RRR), best seen with 325mg per day and 4 weeks of continuous use. The study in the meta-analysis that showed the highest benefit (a 50% reduction in cramps in half of the patients studied) was by Connolly et al., consisting of male veteran patients.[6] The higher benefit reported in the VA study may be explained by the high dose of 500 mg/day, as well as a greater cramp frequency (37 cramps per month compared to an average of 20 per month in the other trials).

The same authors repeated the meta-analysis in 1997, adding non-published studies submitted to the FDA from interested parties. While there was still a 21% RRR with quinine use for leg cramps, the unpublished studies used shorter treatment periods and lower dosages, possibly attributing to the smaller benefit.[7]

III. Dosage and Administration

Quinine sulfate is available by prescription as a 260 mg tablet, and 200 mg and 325 mg capsules. Quinine is also available over–the–counter in many unregulated herbal products. To prevent nocturnal leg cramps, quinine may be taken orally 1-3 hours before bedtime (best with a meal to minimize gastrointestinal irritation). In the meta-analysis by Man-Son Hing et al, doses of 325mg per day were shown to be effective after 4 weeks of continuous use.[5]

IV. Warnings/Adverse Events

Due to the high prevalence of leg cramps in veteran patients, several authors have reviewed quinine's safety and effectiveness in this population.[1, 6, 8, 9] Quinine is protein bound and primarily metabolized in the liver by cytochrome P450, therefore toxicity may occur in renal and hepatic impairment.[8]

A recent report indicates 11% of 132 consecutive patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome or TTP-HUS (in central western Oklahoma's TTP-HUS registry) since July of 1995 were associated with quinine.[10] The authors describe quinine's toxicity as immune-mediated with an explosive onset, and all patients reported quinine use for nocturnal leg cramps on and off for many years. Of note, all the patients were women, despite the fact that leg cramps are common in men. In a second recent

article the same group compiled the clinical features of 39 previously reported cases of quinine induced TTP-HUS, including the initial cases by Gottschall et al.[11] that established TTP-HUS as a new clinical entity. Of the cases, 87% were women, and a common presentation in all the cases was chills and fever with abdominal pain, nausea, vomiting, diarrhea, and oliguria.[12] They also make a case for the urgent diagnosis of TTP-HUS, citing a remission rate of over 80% for patients receiving prompt treatment, versus a 90% fatality rate prior to the availability of plasma exchange for immediate treatment. Recently, a case of reversible pulmonary infiltrates possibly induced by quinine was published.[13] There are reports of repeated episodes of TTP-HUS in patients who took quinine on different occasions [14]; therefore any patient with a history of immune mediated thrombocytopenia or G-6-PD deficiency should not be given quinine. A complete database describing all of the above referenced group's case reports can be found at http://moon.ouhsc.edu/jgeorge

Quinine has quinidine-like activity and may cause cardiotoxicity. Quinine sulfate crosses the placenta, is excreted in breast milk, and has been implicated in stillbirths and birth defects; therefore quinine is labeled pregnancy category X.

V. Monitoring Parameters[15]

Quinine has been associated with significant adverse events including TTP-HUS after as little as a single dose, which can result in chronic renal failure and death if not recognized early. Commonly patients with TTP-HUS presented with chills and fever with abdominal pain, nausea, vomiting, diarrhea, and oliguria.[12] Neurologic as well as laboratory abnormalities such as leukopenia, disseminated intravascular coagulation, and liver function were also present in over a third of the 39 cases reported.[12] Due to its availability as a nutritional supplement, beverage, and by prescription for malaria, clinicians and patients need to be aware of the adverse events associated with quinine use, alternative therapies, and the signs and symptoms of toxicity.

Quinine has a long half-life, is protein bound, and metabolized by the cytochrome P450 system; therefore careful monitoring for drug interactions as well as hepatic or renal impairment is justified.

DRUG	EFFECT	CONSIDERATIONS
Aluminum-containing antacids	↓ Quinine	Aluminum-containing antacids decrease the absorption of quinine.
Quinine	↑ Oral anticoagulants	Quinine may enhance the effects of warfarin and other oral anticoagulants by depressing the hepatic synthesis of vitamin k dependent clotting factors.
Cimetidine	↑ Quinine	Cimetidine may decrease the elimination of quinine and cause toxicity.
Quinine	↑ Digoxin	Increased levels of digoxin have been found with quinine administration; digoxin levels should be monitored in patients taking this combination.
Mefloquine	↑ Quinine	Mefloquine and quinine use can cause ECG abnormalities and cardiac arrest.
Quinine	↑ Neuromuscular blocking agents	Neuromuscular blocking agents (depolarizing and nondepolarizing) may be potentiated and cause respiratory problems.
Quinine	↑ Succinylcholine	Quinine may decrease cholinesterase activity, slowing the metabolism of succinylcholine.
Rifamycins	↓ Quinine	Rifamycins increase the clearance of quinine.
Urinary alkalinizers	↑ Quinine	Urinary alkalinizers (acetazolamide, sodium bicarbonate) may increase quinine blood levels and cause toxicity.

Adapted from Drug Facts and Comparisons, April 2001.[15]

VI. Alternative Therapies for Nocturnal Leg Cramps

Leg cramps are defined as sudden painful involuntary maximal contractions of a muscle or group of muscles in a person without other neurologic or muscle pathology. [8, 16] Cramps are differentiated from claudication by palpable hardening of the muscle, and can last for up to 10 minutes.[8, 16] Clinicians may consider some of the possible causes of leg cramps, and after thorough history and examination can complete a diagnosis (refer to Tables 1 and 2). Stretching the calf muscle by placing the foot in dorsiflexion is the most widely accepted therapy for leg cramps.[17, 18, 19] Refer to Appendix 1 for a patient handout on stretching exercises.

Table 1. Possible causes of leg cramps

Congenital	McArdle's disease (glycogen storage disease), autosomal dominant cramping disease
Endocrinologic	Thyroid disease, diabetes mellitus, Addison's disease
Fluid and electrolyte disorders	Hypocalcemia, hyponatremia, hypomagnesemia, hypokalemia and hyperkalemia, chronic diarrhea, hemodialysis
Neuromuscular disorders	Nerve root compression, motor neuron disease, mononeuropathies, polyneuropathies, dystonias
Vascular disorders	Peripheral vascular disease
Toxins	Lead or strychnine poisoning, spider bite
Drugs	Calcium channel blockers (nifedipine), diuretics, phenothiazines, fibrates, selective estrogen receptor modulators (raloxifene), ethanol; morphine withdrawl
Occupational	Focal dystonias; commonly develop writers, athletes, miners, and musicians
Other	Diarrhea, liver cirrhosis, chronic alcoholism, sarcoidosis

Table 2. Differential diagnosis of leg cramps

Restless leg syndrome	Crawling, creeping sensation in the legs that compels the patient to keep the legs in motion or get up and walk to attain symptomatic relief
Periodic leg movements	Characterized by slow rhythmic extensions of the big toe and occasionally dorsiflexion of the foot during non-rapid-eye-movement sleep
Peripheral neuropathy	Paresthesias and burning sensations in the feet, especially in diabetics; sometimes accompanied by mostly nocturnal cramps
Claudication	Caused by vascular compromise in the lower extremities; may present with muscle cramps during exercise, at rest, or during sleep
Hypnagogic muscle jerking	Normal phenomenon characterized by sudden muscle movements when the individual is falling asleep

While quinine's exact mechanism in the treatment of leg cramps in unknown, it is thought to decrease the excitability of skeletal muscle. Numerous studies were performed after quinine lost its FDA indication, and despite their limitations and varied determinants of efficacy, quinine remains the most widely used treatment for leg cramps (refer to Table 3). While other therapies have been investigated, they have not proven successful for this painful and chronic condition.[19]

In special populations, there has been limited success with alternative agents for leg cramps. Vitamin E 800 IU/day was not superior to quinine 500 mg/day or placebo in a study of male veterans[6]; however 400 IU/day was shown to be as effective as quinine 325 mg/day in patients on dialysis.[20] Additionally, vitamin B complex has been shown effective in elderly hypertensive patients.[21] While magnesium has been used in pregnant women with success, two double-blind placebo-controlled trial in the general population showed no effect.[22, 23]

Table 3. Published studies of quinine for reducing leg cramps in non-dialysis patients

STUDY	DESIGN	N	INCLUSION	DRUG	DOSE	DURATION	RESULTS	4 WEEK CRAMP BENEFIT*
Jones et al[24]	rdbpc, crossover	9	≥2 cramps/week	quinine sulfate	300 mg hs	2 weeks	p<0.01	-4.0
Waburton et al[25]	rdbpc, crossover	22	>2 cramps/week	quinine bisulfate	300 mg hs	3 weeks	NS	-4.06
Fung et al[26]	rdbpc, crossover	8	>2 cramps/week	quinine sulfate	200 mg hs	4 weeks	p<0.01	-7.37
Connolly et al[6]	rdbpc, crossover	27	≥6 /month	placebo, vitamin E, or quinine sulfate	500 mg pm	4 weeks	p=.0046	-17.56 vitamin e had no effect
Siderov[27]	rdbpc, crossover	16	>2 cramps/week	quinine sulfate	200 mg hs	2 weeks	NS	-1.37
Man-Son Hing et al[5] meta-analysis (included above 5 trials)	**meta-analysis**	**107**	**rdbpc, crossover trials**	**quinine**	**200-500 mg qd**	**4 weeks**		**-8.3 95% CI (3.85 to 12.75)**
Dunn[28]	rdbpc, crossover	25	quinine use	quinine sulfate	300 mg hs	4 weeks	31% (# n/a) fewer cramps p<0.01	n/a
Jansen[29]	rdbpc parallel	102	≥3 cramps/week	hydroquinine	300 mg q pm	2 weeks	36% or 8 fewer cramps (95%CI7-12)	n/a
Diener[30]	rdbpc, parallel	98	>6 in 2 weeks (average of 12)	quinine	400 mg	2 weeks	8 fewer cramps (95%CI7-10)	n/a

rdbpc=randomized, double-blind, placebo-controlled
*Calculated in Man Son Hing meta-analysis by obtaining further individual patient data and doubling 2-week data to standardize to a 4–week treatment period.

VII. Recommendations for Use of Quinine for Nocturnal Leg Cramps

Although serious adverse events associated with quinine appear to be rare, there continue to be reports linking this medication to severe, life threatening reactions. Conversely, while nocturnal leg cramps are a common and troubling condition for veteran patients, they are not associated with severe medical outcomes. Therefore, use of quinine for nocturnal leg cramps should be reserved for patients who have failed other modalities, and who have severe symptoms that require treatment. Patients should be advised of the potential for rare adverse drug reactions to quinine.

VIII. References

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